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20 February 2019

The Diabetes Subcommittee of PTAC
c/o PHARMAC
PO Box 10254
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Dear Committee & Colleagues

Re: Diabetes therapeutics in Aotearoa New Zealand for consideration in the upcoming Diabetes Subcommittee of PTAC meeting, scheduled for March 2019

On behalf of the New Zealand Society for the Study of Diabetes (NZSSD) executive, I am writing to raise a number of concerns from clinicians regarding the state of diabetes therapeutics in New Zealand. These concerns have been aired with The Honourable Dr David Clark, Minister of Health, and also with The Honourable Steve Maharey, PHARMAC Board Chair, and Sarah Fitt, Chief Executive of PHARMAC, in a meeting held on 7 December 2018. Our members and Society have raised many of them previously (see attached)

The key points in summary (these points are further explained on the following pages):

Executive summary:

1) Access to a number of therapeutic agents and devices for diabetes in NZ, and their optimal use is markedly inadequate and now lags well behind nations of comparable standards of healthcare, in particular Australia, Canada, and the United Kingdom.

2) Type 2 diabetes, in particular, is increasing in number and diabetes control is poor in NZ, resourcing is weighted too heavily in the treatment of established renal and cardiovascular disease compared to the lack of therapeutic agents to improve glucose control.

3) We need to better engage in meaningful dialogue with clinicians, reducing clinical inertia and reducing delays in effective treatment options which are vital for this large sector of people in NZ with diabetes.

Our principal concerns relate to due process, lack of clinical engagement by PHARMAC with relevant groups, managing clinical discussion and decisions within PHARMAC, consequent delays and growing treatment gaps, and the consequences of this for both individual patient care and equity of care in New Zealand.

It is important to emphasise that the role of PHARMAC, based on its own terms of reference and public statements are:

1. *Access, including equity of access to medicines;*
2. *Optimal use of medicines and medicines are used to their best effect;*
3. *Quality of medicines that are safe and effective.*

Access to a number of therapeutic agents and devices for diabetes in NZ, and their optimal use, is markedly inadequate and now lags well behind nations of comparable standards of healthcare, in particular Australia, Canada, and the United Kingdom.

In contrast to this lack of access to therapeutics, treatment of significant diabetes-related complications such as renal failure or heart disease, is provided in a way comparable to that provided in those other OECD countries, despite being very costly.

Context:
Within New Zealand there has been a growing appreciation of the enormous number of patients with type 2 diabetes (T2DM) through widespread diabetes screening encouraged by health policy in New Zealand. Furthermore, there are marked disparities in rates, control and complications of diabetes by ethnicity and social deprivation. The best national figures we have regarding overall glucose control in New Zealand compare poorly with data from Australia (AusDiab data). This will be very familiar to clinicians working in the diabetes field, including those within the PTAC Subcommittee.

For many years New Zealand has had a very limited pharmacopoeia to manage T2DM. Prior to October 2018, the last novel funded medication for T2DM was Pioglitazone which was approved in 2004. The special authority criteria were broadened in 2007 without any obvious involvement of the Diabetes Subcommittee of PTAC of that time. In the 14 years since the Diabetes Subcommittee of PTAC has been asked for their view of new agents to consider under PHARMAC's budget. Minutes from that subcommittee have shown they repeatedly rated these newer agents as moderate or high priority, and repeatedly PTAC has reduced the priority to "low".

In contrast, once renal failure ensues or a cardiac event occurs, people with T2DM will receive state of the art expensive therapies including renal replacement therapy, retinal lasering or intravitral injection therapy, renal transplant or coronary revascularisation at rates similar to patients in Australia. To access these therapies they must first become severely unwell with consequent loss of earning potential for many, reduction in quality of life or dying. Primary care has limited effectiveness in preventing complications, and secondary care/specialist services are burdened managing the complications.

Process:
It is noted that PTAC does not have any specialist clinician expertise in diabetes or in cardiovascular or renal disease.

The Diabetes Subcommittee of PTAC last met on 10 October 2016. PTAC has subsequently met four times. The first of these, in February 2017, considered the Diabetes Subcommittee of PTAC minutes, the next meeting in November 2017 chose to defer any change of priority of an SGLT2 inhibitor from the low priority it had previously given, the February 2018 meeting deferred consideration of long acting glargine insulin to the Diabetes Subcommittee, and the May 2018 meeting deferred a decision of funding Liraglutide to the Diabetes Subcommittee.

In all of this time, despite these active proposals and considerations, the Diabetes Subcommittee of PTAC has not been called to meet to progress any of these matters on PHARMAC's own agenda, let alone any other matters that expert committee might think appropriate. This seems an error of process, and a lack of appreciation of the urgency and unmet need of treatment for people with T2DM in New Zealand.

In contrast to that inactivity and inertia, PHARMAC have made no fewer than three major changes to the clinical provision of diabetes products or devices in the time since the Diabetes Subcommittee last met in 2016.

The first of these relates to a wholesale change in glucose meters and ketone testing approach within New Zealand. We are aware that the meters etc. were considered by the Diabetes Subcommittee of PTAC and as a professional society (NZSSD) we met with the then Chief Executive of PHARMAC, Mr Steffan Crausaz, on 15 November 2017 along with Ms Lisa Williams and Ms Janet Mackay. The NZSSD was concerned with the prior roll-out of meter changes and the proposed changes to ketone testing and indicated its willingness to work with PHARMAC for the purpose of implementation and any problem-solving regarding a number of matters which we highlighted. We were informed that we

would be contacted regarding that and that collaboration would be welcome (but this never occurred). Certain implementation issues and concern regarding the accurate operation below ambient temperatures common in NZ remain unresolved.

The second major change is the listing of a new DPP-4 inhibitor, Vildagliptin. We have already covered some of our concerns in response to the consultation document released in July 2018 regarding the funding of this agent. We trust that the Diabetes Subcommittee of PTAC will be provided with this in correspondence, along with other feedback relevant to that proposal. This agent was bundled along with a number of other agents by Novartis in a proposal for funding. Novartis had not been actively promoting this agent previously in NZ, and whilst it has been promoted elsewhere, they are no longer marketing its use in Australia. PHARMAC notified the public on 6 September regarding the funding of Vildagliptin (as a single agent or in combination with Metformin) effective 1 October, i.e. less than one month later. The process of consideration, approval, and funding of Vildagliptin appears to be in conflict with the processes that PHARMAC states it holds strongly:

- Firstly, there was minimal consultation with the sector apart from the consultation document, and there is no evidence that the Diabetes Subcommittee of PTAC or professional bodies dealing with diabetes were formally engaged in that decision. PTAC, which presumably did consider the proposal, do not have the requisite expertise within the committee in our opinion.
- Secondly, Vildagliptin is notable in the class of DPP-4 inhibitors as not being FDA approved [1]. This is on a background of PHARMAC repeatedly delaying decisions to fund a number of the novel agents including others in the DPP-4 class (and also GLP-1, and SGLT2 agents) pending FDA review of required trials of the cardiovascular safety of these newer agents (these are for agents which are already FDA approved). Additionally, PHARMAC appears to have been misinterpreting the purpose of the FDA mandated safety studies.[2]

Thus, PHARMAC's only new funded glycaemic treatment for T2DM in 14 years is one that has not been subjected to the standards of FDA approval and in fact was flagged by the FDA as having some potential concerns more than a decade ago. This suggests that PHARMAC has not followed its own process. Important factors seem to have been unappreciated; this could have been avoided by more substantial dialogue, including using PHARMAC's own existing expert subcommittee.

The third major change was a change of insulin pump suppliers for patients with type 1 diabetes, which was announced by PHARMAC on 16 October 2018 , becoming effective on 1 November 2018. We believe that PHARMAC appreciates that considerable expertise in multidisciplinary specialist clinical teams is required to effectively support and manage patients with pumps. Improvements, including newer generation pumps, are welcomed by the sector, but wholesale changes require sector engagement and longer lead times to become proficient in the new technology; to be able to offer expert unbiased advice regarding pump choice, for expert clinical oversight and advice, and to schedule patients to safely transition from existing hardware. This is often a time-critical issue for patients with type 1 diabetes for their safety and to achieve and maintain the sort of clinical improvements required to maintain approval for continued funding of their pumps and consumables. The service requirements for this are considerable and in many cases require clinician and patient re-training, additional patient review, with the new pumps. Again, the Diabetes Subcommittee of PTAC

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1 The history on this is complicated, but essentially the EMA had approved its use in combination with other antidiabetic medications in the early 2000's and in March 2006 Vildagliptin was accepted to be reviewed by the FDA. However, in 2007 the FDA requested Novartis to conduct a new study to assess the safety and efficacy of it in patients with impaired kidney function. Data was presented by the manufacturer in November 2007 and in view of concerns regarding safety, approval of vildagliptin was not given by the FDA. To our knowledge, it remains unapproved as the requisite data/studies required by the FDA have never being performed or met.

2 The context is cardiovascular safety of ultra-intensive management of glycaemia in patients with type 2 diabetes following several high profile studies reported in 2008. The FDA has mandated closer scrutiny of the newer agents, although they have remained as funded registered treatments within that country (USA) in the interim. These studies have been performed as non-inferiority studies, principally to assess safety of the agents rather than as superiority studies to show any incremental benefit agent vs agent as each was compared with more "traditional" treatments (often comparison with placebo with additional open label therapy to reach a given glycaemic target for example)

appears to not have been convened or its members contacted for advice regarding this. The decision has essentially been “commercial”.

Growing gaps:
The delay to convene the Diabetes Subcommittee of PTAC until well after four PTAC meetings, each with diabetes agenda items, does not serve medical need for people with diabetes. It adds to clinical inertia, at the highest level, delaying effective treatment options.

There is concern regarding the current state of overall glucose control (not to mention renal protection and cardiovascular disease management) in patients with T2DM in New Zealand. The lack of acceptable funded options remains a concern. Requirements for appropriate agents are those:

a) that do not cause further weight gain in populations known to be obese,

b) with a low risk of hypoglycaemia in people who are fearful of this or when it may impact upon current or future prospects for employment,

d) that are acceptable to the generalist clinicians who are managing clinical care in the bulk of patients with T2DM (primary care doctors, nurse practitioners etc.) who remain concerned and somewhat uncertain about the use of insulin with its known side effect profile[3].

Guidance of course has been limited in recent years due to the dissolution of the New Zealand Guidelines Group in approximately 2013. The NZSSD has written directly to PHARMAC regarding this, in particular asking how PHARMAC plan to support the rollout of “Galvus” (vildagliptin). Danae Staples-Moon responded by email on 23 October 2018 saying “it is not PHARMAC’s role to create clinical guidelines, so PHARMAC will not be producing any”. The NZSSD believe that appropriate guidance is essential for proactive management of chronic conditions such as diabetes and to achieve “optimal use of medicines and medicines are used to their best effect”. We have the weight of opinion on our side with an international Consensus regarding this, and feedback across our membership who provide advice, support and education for generalists such as GPs/NPs wanting simple, accessible advice to help manage patients who do not meet therapeutic targets.

PTAC have deferred decisions regarding funding new treatments pending the receipt of international guidelines (paragraph 1.6, minutes of PTAC meeting held 9-10 February 2017).

International guidance now exists, and has been widely accepted. As presented to The Honourable Steve Maharey and Ms Sarah Fitt, guidance on management of hyperglycaemia in T2DM has been recently updated with a Consensus report by both the American Diabetes Association and the European Association for the Study of Diabetes and published in the highest impact diabetes journals in the world. (ePublished online in Diabetes Care on 4 October 2018.) As members of Diabetes Subcommittee of PTAC will know, this guidance has been seen as a major step forward to promote evidence-based incremental therapies, prioritised around patients’ needs and clinical issues. These particularly highlight cardiovascular disease and kidney disease, issues of high prevalence in our population, (especially in Māori and Pacific peoples); risks of hypoglycaemia and concern regarding weight gain. However, following this guidance is problematic in New Zealand as the only pathway that one can follow with funded medications is the sub-optimal route recommended only when “cost is a major issue”, and even that approach is only suggested for those without established cardiovascular or renal disease. For those with cardiovascular or renal disease there is “nowhere to go”.

The authors of the Consensus note the risk of “creating a two tiered system of treatment” (read “disparity”) and state further that “since glycaemic management remains a cornerstone of the prevention of diabetes complications, these disparities rae questions of fairness, equity and overall public health”. These criticisms directly expose the situation in New Zealand.

The sector including the Diabetes Subcommittee of PTAC (based on its minutes) has been reassured that a Health Economic Model for diabetes and resulting cost-utility analysis to help “re-prioritise“ the “new” antidiabetic agents is underway. This has been promised for several years (before October 2016), but there has been no evidence of any progress since. Whatever this delay to “re-prioritise” may be saving PHARMAC’s budget, it is costing other sectors of the health system funded by

3 Hypoglycaemia due to sulfonylureas and insulin is the second most common cause for medication-related admissions to hospitals in developed nations, as one example.

Government and it is costing lives. In New Zealand this population is disproportionately poor, Māori and Pacific. Inertia around decision making is coming at a large human cost.[4]

We implore PHARMAC to deliver on its stated aims for this group of New Zealanders, to follow due process for better treatments, not to delay treatment decisions and push cost to managing complications, and to better engage in meaningful dialogue with clinicians including, but not limited to, the Diabetes Subcommittee of PTAC.

Kind regards

Yours Sincerely

Dr. Brandon Orr-Walker**,**
President NZSSD, on behalf of the Executive

cc The Honourable Steve Maharey
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Enc:
Appendix 1 Editorial NZMJ 10 June 2016, Vol 129 No 1436
Appendix 2 NZSSD Pharmac submission re Vildagliptin

4 As an example, over a 4 years of "deliberation" 50% of patients with nephropathy will have halved their renal function, commenced dialysis, or died, despite renal protective therapy with RAS blockade but without SGLT-2 inhibitors (RENAAL study, N Engl J Med, Vol. 345, No. 12 September 20, 2001).